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ning of each regular issue of the PCT Gazette.

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(54) Title: USE OF HMGB1 IN THE TREATMENT OF TISSUE DAMAGE AND/OR TO PROMOTE TISSUE REPAIR

(57) Abstract: It is described a composition comprising an effective amount of the HMGB1 protein or functional parts thereof, or HMGB1 expressing vectors, for the treatment of tissue damage and/or to promote tissue repair and regeneration. It is further described a composition comprising an effective amount of an antagonist of the HMGB1 protein for the treatment of adverse effects induced by necrotic tissue, such as recruitment and activation of myeloid cells, loss of the barrier function of endothelia, edema.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K16/18 A61K39/395 A61P9/10 A61P29/00 C07K14/47
A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, MEDLINE, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 00 47104 A (PICOWER INST MED RES) 17 August 2000 (2000-08-17) page 3, line 19 - line 37 page 6, line 16 - line 38 page 10, line 27 -page 11, line 9 page 11, line 10 - line 22 example 6 --- | 11-15 |
| X | WO 01 89526 A (NORTH SHORE LONG ISLAND JEWISH) 29 November 2001 (2001-11-29) page 2, line 8,12,13,25 page 32; example 4 --- -/- | 11-14 |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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- °X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- °Y° document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Irion, A

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| X | FANG WEN-HUI ET AL: "The significance of changes in high mobility group-1 protein mRNA expression in rats after thermal injury." SHOCK (AUGUSTA, GA.) UNITED STATES APR 2002, vol. 17, no. 4, April 2002 (2002-04), pages 329-333, XP009020804 ISSN: 1073-2322 abstract --- | 11,13,14 |
| X | FAGES C ET AL: "REGULATION OF CELL MIGRATION BY AMPHOTERIN" JOURNAL OF CELL SCIENCE, ESSEX, GB, vol. 113, no. 4, February 2000 (2000-02), pages 611-620, XP001070170 abstract --- | 16-18 |
| X | MULLER SUSANNE ET AL: "The double life of HMGB1 chromatin protein: Architectural factor and extracellular signal" EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 20, no. 16, 15 August 2001 (2001-08-15), pages 4337-4340, XP002261324 ISSN: 0261-4189 page 4338, right-hand column, paragraph 3 - paragraph 4 --- | 16-18 |
| X | WANG HAICHAO ET AL: "HMGB1 as a late mediator of lethal systemic inflammation" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, vol. 164, no. 10 Part 1, 15 November 2001 (2001-11-15), pages 1768-1773, XP002261325 ISSN: 1073-449X the whole document --- | 11-15 |
| X | WANG H ET AL: "HMG-1 AS A LATE MEDIATOR OF ENDOTOXIN LETHALITY IN MICE" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, US, vol. 285, 9 July 1999 (1999-07-09), pages 248-251, XP002940163 ISSN: 0036-8075 cited in the application the whole document --- | 11-15 |
| | | -/- |

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| P,X | WO 02 092004 A (GEN HOSPITAL CORP ;YANG HUAN (US); FINK MITCHELL P (US); TRACEY KE) 21 November 2002 (2002-11-21) page 3, line 20 - line 30 page 6, line 8 - line 22 page 7, line 1 - line 6 page 8, line 3 - line 7 page 14, line 15 - line 17 page 13, line 1 - line 7 page 16, line 1 - line 3 page 23, line 5,6,15,17 page 28, line 6 - line 10 page 31, line 4 - line 8 page 30, line 19 - line 20 examples 5-7,12,13 --- | 1-18 |
| P,X | WO 02 074301 A (FINK MITCHELL P ;TRACEY KEVIN J (US); ULLOA LUIS (US); UNIV PITTSB) 26 September 2002 (2002-09-26) the whole document --- | 11-15 |
| P,X | YANG HUAN ET AL: "HMGB1 as a cytokine and therapeutic target." JOURNAL OF ENDOTOXIN RESEARCH, vol. 8, no. 6, 2002, pages 469-472, XP009020930 ISSN: 0968-0519 the whole document --- | 11-14 |
| P,X | SCAFFIDI PAOLA ET AL: "Release of chromatin protein HMGB1 by necrotic cells triggers inflammation" NATURE (LONDON), vol. 418, no. 6894, 11 July 2002 (2002-07-11), pages 191-195, XP002261326 ISSN: 0028-0836 the whole document --- | 11-15 |
| A | WO 97 23611 A (BULLERDIEK JOERN) 3 July 1997 (1997-07-03) abstract page 21, line 24 - line 31 page 20, line 29 - line 36 page 12, line 52 - line 53 page 11, line 57 - line 65 page 10, line 33 - line 34 page 5, line 53 - line 55 --- | 1-10, 16-18 |
| | | -/- |

INTERNATIONAL SEARCH REPORT

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| PCT | 03/00265 |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| A | <p>YANG R ET AL: "ETHYL PYRUVATE MODULATES INFLAMMATORY GENE EXPRESSION IN MICE SUBJECTED TO HEMORRHAGIC SHOCK" AMERICAN JOURNAL OF PHYSIOLOGY: GASTROINTESTINAL AND LIVER PHYSIOLOGY, AMERICAN PHYSIOLOGICAL SOCIETY, US, vol. 283, 2002, pages G212-G221, XP008019310 ISSN: 0193-1857</p> <p>-----</p> | |
| A | <p>SIMS C A ET AL: "RINGER'S ETHYL PYRUVATE SOLUTION AMELIORATES ISCHEMIA/REPERFUSION-INDUCED INTESTINAL MUCOSAL INJURY IN RATS" CRITICAL CARE MEDICINE, WILLIAMS AND WILKINGS COMPANY, BALTIMORE, MA, US, vol. 29, no. 8, 2001, pages 1513-1518, XP008019328 ISSN: 0090-3493</p> <p>-----</p> | |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IT 03/00265

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 16-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple Inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No

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| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|--|------------------|
| WO 0047104 | A 17-08-2000 | US 6303321 B1 | | 16-10-2001 |
| | | AU 3698300 A | | 29-08-2000 |
| | | CA 2359926 A1 | | 17-08-2000 |
| | | EP 1165110 A2 | | 02-01-2002 |
| | | JP 2003520763 T | | 08-07-2003 |
| | | WO 0047104 A2 | | 17-08-2000 |
| | | US 2003017155 A1 | | 23-01-2003 |
| | | US 2003113323 A1 | | 19-06-2003 |
| | | US 2003143194 A1 | | 31-07-2003 |
| | | US 6468533 B1 | | 22-10-2002 |
| | | US 2002102609 A1 | | 01-08-2002 |
| WO 0189526 | A 29-11-2001 | US 2002016344 A1 | | 07-02-2002 |
| | | AU 6162901 A | | 03-12-2001 |
| | | CA 2408791 A1 | | 29-11-2001 |
| | | EP 1307196 A1 | | 07-05-2003 |
| | | WO 0189526 A1 | | 29-11-2001 |
| WO 02092004 | A 21-11-2002 | WO 02092004 A2 | | 21-11-2002 |
| | | US 2003060410 A1 | | 27-03-2003 |
| | | US 2003144201 A1 | | 31-07-2003 |
| WO 02074301 | A 26-09-2002 | WO 02074301 A1 | | 26-09-2002 |
| WO 9723611 | A 03-07-1997 | DE 19548122 A1 | | 26-06-1997 |
| | | AU 1870597 A | | 17-07-1997 |
| | | CA 2239682 A1 | | 03-07-1997 |
| | | WO 9723611 A2 | | 03-07-1997 |
| | | EP 0870024 A2 | | 14-10-1998 |
| | | JP 20000504933 T | | 25-04-2000 |
| | | NZ 504445 A | | 28-08-2002 |
| | | US 6323329 B1 | | 27-11-2001 |
| | | US 2002120120 A1 | | 29-08-2002 |